UNITED STATES DEPARTMENT OF COMMERCE
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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/321,987	05/28/99	KIMBLE J	960296.95386

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EXAMINER	
SHUKLA,R	
ART UNIT	**PAPER NUMBER**
1632	14

DATE MAILED: 07/03/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 09/321,987	Applicant(s) KIMBLE ET AL.	
	Examiner Ram Shukla	Art Unit 1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 April 2001* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-10 and 13* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-10 and 13* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☒ The proposed drawing correction filed on *05-28-99* is: a)☐ approved b)☒ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☐ Notice of References Cited (PTO-892)
16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
18) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other: .

DETAILED ACTION

1. Amendment filed 4-19-01 has been entered.

2. Claims 11, 12, and 14-27 have been canceled.

3. Amendments to claims 1-8 and 13 have been entered.

4. Claims 1-10 and 13 are pending.

Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures

5. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 C.F.R. § 1.821(a)(1) and (a)(2) (see claims 52 and 55 and the specification on pages 19 and 64). However, this application fails to comply with the requirements of 37 C.F.R. §§ 1.821-1.825 .

The specification on page 9, line 3 and figure 1C disclose amino acid sequences, however, these sequences have not been listed in the sequence listing.

Response to Arguments

Applicants response to the amino acid sequence disclosure is not sufficient to address sequence compliance requirement because although Applicants have added sequences to the sequence listing, they have not modified the specification to identify the sequences cited in the previous office action (for example, on page 9) by sequence identifier.

Applicants are required to make appropriate amendment to the specification to identify the nucleotide and amino acid sequences by sequence identifiers.

Claim Rejections - 35 USC § 112

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 6-10 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention, for reasons of record set forth in the previous office action of 12-13-00.

Response to Arguments

Applicants have argued that Applicant's disclosure fully encompasses the scope of the protein as recited and direct to pages 11 and 17 for description, however these arguments are not persuasive because the indicated parts of the specification are general statements about the assay, not a description of the recited proteins. Applicants further argue that an artisan can use the disclosed system without undue experimentation to assess whether a protein meets the sequence identity criteria. Further, Applicants argue that a cDNA for human aggrecanase when introduced in a gon-1 mutant worm partially rescued these worms such that some animals exhibited some cell migration and that this example meets the criteria of claim 6. However, Applicant's arguments are not persuasive because the assay recited in claim 1 is for identifying a compound that modulates the activity of a protein that directs the migration of a gonadal cell, whereas the assay described by the Applicants is for identifying a protein that rescues the migration of a gonadal cell in a nematode in which a gonadal cell does not migrate. Therefore, the results discussed by the Applicants are not relevant to the instantly claimed method of claim 6.

In summary, the limited information in the specification is not deemed sufficient to reasonably convey to one skilled in the art that Applicant is in possession of sequence structure of the homologues of the proteins that comprises a metalloprotease domain and a thrombospondin domain, or that have 20% sequence similarity with said target protein, or any and all chimeric proteins at the time the application was filed. Thus it is concluded that the written description requirement is not satisfied for the claimed genus.

8. Claims 1-10 and13 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention, for reasons of record set forth in the previous office action of 12-13-00.

Response to Arguments

Applicant's arguments filed 4-19-01 have been fully considered but they are not persuasive. Applicants have argued that the specification teaches that gon-1 is essential for extension of gonadal germline arms and that in C.elegans hermaphrodites, gon-1 is required for migration of distal tip cells to produce two elongated tubes whereas in males, it is required for migration of a single linker cell to produce a single elongated tube. However, these arguments are not persuasive because these statements do not indicate that a modulatory compound that alters migration of gonadal cell would do so by altering the activity of gon-1. For example, a modulatory compound that would cause apoptosis of gonadal cell would alter gonadal cell migration without affecting gon-1 protein. Therefore, just because gon-1 is essential for gonadal cell migration does not indicate that a compound that alters migration of gonadal cell would also indicate that the compound alters the activity of gon-1.

Applicants further argue that their method can be used in systems in which a gon-1 substitute protein is used in the assay. Again, these arguments are not persuasive because claims 6-10 would require first determining whether any of the recited proteins would have affected the gonadal cell migration in the first place, before a compound can be identified and the instant claim 1 does not recite any such step. It is noted that the specification except for teaching gonadal cell migration does not teach any assay that would show that the activity of a compound or a protein would rescue or alter gon-1, not any other gene . Applicants have argued that some amount of gon-1 is essential for any cell migration and because the test compares cell migration activity, it is irrelevant

whether the potential modulator has any effect upon the migration protein. Again these arguments are not persuasive because the preamble of claim 1 recites that the method is for screening a compound that alters the activity of a protein that directs the migration of gonadal cell, and therefore, while the phenotype is a change in migration of gonadal cell, the compound alters the activity of a protein that in turn directs migration of gonadal cell and the specification does not teach that change of gonadal cell migration in claim 1 would be only because of gon-1, therefore, a compound that alters gonadal cell migration would alter gon-1 activity. It is reiterated that the invention of claim 1, as instantly recited, is directed to a method of identifying a compound that modulates an activity of a protein that directs the migration of a gonadal cell, and not to a method of identifying a mutant of gon-1 because such mutant would not alter the activity of another gon-1 protein.

Applicants have further argued that it is irrelevant whether the recited proteins would naturally have the activity of a metalloprotease or a thrombospondin because the system provides a mechanism for assessing the activity of metalloprotease/thrombospondin motif in the system. Again these arguments are not persuasive because the specification does not teach that the change in migration is due to the metalloprotease/thrombospondin motif. For example, as discussed in the previous office action, Kuno et al described ADAMTS-1 as a gene highly expressed in vivo in colon 26 cachexigenic tumor (Kuno K et al. The J of Biological Chemistry 274:18821-18826, 1999). While it has been shown that ADAMTS-1, a member of ADAMs family of proteins, is incorporated in ECM, there is not evidence that this protein has a role in gonadal cell migration. Furthermore, the metalloprotease motif of ADAMTS-1 is inactive due to the lack of Zinc-binding motif (see the introduction section in columns 1 and 2 on page 18821) therefore, it is not clear whether ADAMTS-1 will have the characteristic metalloprotease activity of this class of molecules or even be functional in C.elegans or would have gon-1 function. Thus if ADAMTS-1 does not have biological activity in C.elegans, how can it alter a gonadal cell migration. Likewise, there is no evidence whether other two metalloproteases would also have the gon-1 like activity and therefore, it is not clear whether one can call these recited

metalloproteases true homologues of gon-1 when the only known similarity is in the sequence and no functional similarity is known. It is further noted that the Colige et al (Colige A et al. Proc. Natl. Acad. Sci. USA 94:2374-2379, 1997) reported the cloning and characterization of the bovine procollagen-I N-proteinase. However, they did not describe whether this protein was expressed in gonads (see figure 6 in Colige et al). Again, there is no evidence whether bovine collagenase-I N-protease has any role in gonadal cell migration. Applicants, in the last paragraph on page 5 of their response, noted that human aggrecanase partially rescued gon-1 null mutant such that some animals exhibited some cell migration, however, the response does not provide any particulars of these results as to what fraction of animals exhibited the activity or what fraction of gonadal cells exhibited activity. Therefore, these results can not be evaluated in light of the enablement rejection. In summary, there is no evidence in the specification or in the art to suggest any of the proteins recited in claim 9 has a role in gonadal cell migration. Next, the specification is also not enabling for the target proteins being a fragment or truncated forms of gon-1 or any other recited proteins because there is no evidence whether these embodiments would have had any biological activity that would have affected gonadal cell migration.

Next, Applicants have reiterated that the cell migration activity is not an essential attribute of the protein in the method and therefore, recitation of 20% amino acid sequence identity is enabled. In response it is noted that the activity of the protein is essential because that is what causes the cell migration as discussed above. In summary, the specification is not enabling for the claimed invention because the specification as filed does not provide sufficient guidance, working example and evidence as to how as to how an artisan would practiced the claimed invention without required undue experimentation.

9. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

10. Claims 1-10 and 13 remain rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

It is noted that the claim language is very confusing and there are grammatical errors, due to which relationship of the different parts of a claim is not clear and amendment to the claims has further made the claims indefinite and vague. For example, in claim 1 as instantly recited, it is unclear whether a protein is present in the nematode. Additionally, it is unclear as to what would be considered "a change .....attributable to the presence.." in line 9. Furthermore, while the preamble of the method recites a modulator of an activity of a protein, the steps of the method do not recite any activity of a protein, therefore, there is no nexus between the preamble and the method steps. In case of claim 6, it is noted that while claim 6 recites a markush group of proteins, line 9 of the claim recites that the "polynucleotide sequence being under the control of a promoter....." therefore, it is not clear how different embodiments of the claim are linked to each other.

Claim 6 is vague and indefinite because it recites "a chimeric protein." The metes and bounds of the claim are not clear because it is unclear as what are constituents of the chimeric protein.

Claim 6 recites the limitation "the polynucleotide sequence" in line 9. There is insufficient antecedent basis for this limitation in the claim because line 3 recites a native polynucleotide sequence whereas line 4 recites a heterologous polynucleotide sequence.

Claim 6 is also vague and indefinite because it is unclear as to what would be considered "sufficiently close." Since the term "sufficiently" is a relative term, the metes and bounds of the invention are not clear.

Claim 7 and 8 are vague and indefinite because they recite the phrase "wherein the .....is C.elegans gon-1." It is noted that gon-1 is not a polynucleotide sequence, it is the name of a gene.

11. No claim is allowed.

12. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Applicants are advised to submit a clean version of each amended claim (without underlining and bracketing) according to **§** 1.121(c) and a copy of all the pending/under consideration claims. For instructions, Applicants are referred to http://www.uspto.gov/web/offices/dcom/olia/aipa/index.htm.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ram R. Shukla whose telephone number is (703) 305-1677. The examiner can normally be reached on Monday through Friday from 7:30 am to 4:00 p.m. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Karen Hauda, can be reached on (703) 305-6608. The fax phone number for this Group is (703) 308-4242. Any inquiry of a general nature, formal matters or relating to the status of this application or proceeding should be directed to the Kay Pinkney whose telephone number is (703) 305-3553.

Scott D. Priebe

SCOTT D. PRIEBE, PH.D
PRIMARY EXAMINER

Ram R. Shukla, Ph.D.
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